WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Tuesday, March 07, 2006

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT,EPAB; PLUR=YES; OP=ADJ		
☐	L23	L22 and L12	997
☐	L22	L19 and L9	1045
☐	L21	L20 and L19	3
☐	L20	(roffler or cheng or taipei).in.	19633
☐	L19	(424/138.1 |424/141.1 |424/155.1 |424/179.1 |424/180.1)![CCLS]	2082
☐	L18	4624846.pn.	1
☐	L17	L16 not @ay>1998	61
☐	L16	L10 and L15	592
☐	L15	L12 near4 L13	84303
☐	L14	L12 with L13	204658
☐	L13	accelera$ or enhance$ or increas$	3350129
☐	L12	clearance or cleared or remov$ or excrete$	2827507
☐	L11	anti-polyethylene glycol or (anti-poly(ethylene glycol)) or (anti-poly (ethylene) glycol)	4
☐	L10	L9 with L8	7067
☐	L9	(polyethylene glycol)or PEG or (poly(ethylene) glycol) or (poly(ethylene glycol)) or (methoxypoly(ethylene glycol))	228496
☐	L8	antibod$	162074
☐	L7	antipeg or anti-peg	10
☐	L6	L5 and peg	5
☐	L5	L4 with L2	7
☐	L4	prodrug	29131
☐	L3	L2 and prodrug	29
☐	L2	hydroxyaniline mustard	38
☐	L1	hydroxylaniline mustard	0

END OF SEARCH HISTORY

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Tuesday, March 07, 2006

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,EPAB; PLUR=YES; OP=ADJ	
☐	L10	APG3	6
☐	L9	L8 and prodrug	7
☐	L8	L7 and (clear$ or remov$)	314
☐	L7	L6 not @ay>1999	351
☐	L6	anti$ NEAR2 l5	778
☐	L5	polyethylene glycol	177636
☐	L4	L3 not @ay>1999	1
☐	L3	antipeg or (anti-peg) or (anti peg)	14
☐	L2	6077499.pn.	1
☐	L1	(6617118 or 6596849).pn.	2

END OF SEARCH HISTORY

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1642BJF

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2		"Ask CAS" for self-help around the clock
NEWS 3	DEC 05	CASREACT(R) - Over 10 million reactions available
NEWS 4	DEC 14	2006 MeSH terms loaded in MEDLINE/LMEDLINE
NEWS 5	DEC 14	2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
NEWS 6	DEC 14	CA/CAplus to be enhanced with updated IPC codes
NEWS 7	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform
NEWS 8	DEC 23	New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/ USPAT2
NEWS 9	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS 10	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS 11	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS 12	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS 13	JAN 30	Saved answer limit increased
NEWS 14	JAN 31	Monthly current-awareness alert (SDI) frequency added to TULSA
NEWS 15	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 16	FEB 22	Status of current WO (PCT) information on STN
NEWS 17	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 18	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 19	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 20	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS 21	FEB 28	TOXCENTER reloaded with enhancements
NEWS 22	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS 23	MAR 01	INSPEC reloaded and enhanced
NEWS 24	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes

NEWS EXPRESS FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT http://download.cas.org/express/v8.0-Discover/

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:47:25 ON 07 MAR 2006

=> file medline
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 0.21 0.21

FILE 'MEDLINE' ENTERED AT 10:47:38 ON 07 MAR 2006

FILE LAST UPDATED: 4 MAR 2006 (20060304/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s anti () PEG
        616721 ANTI
             6 ANTIS
        616725 ANTI
                  (ANTI OR ANTIS)
          9879 PEG
           777 PEGS
         10278 PEG
                  (PEG OR PEGS)
L1           7 ANTI (W) PEG

=> s l1 not py>2000
       2953639 PY>2000
                  (PY>20009999)
L2           4 L1 NOT PY>2000

=> d ibib 1-4

L2   ANSWER 1 OF 4     MEDLINE on STN
ACCESSION NUMBER:   2000191525     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 10725103
TITLE:              Efficient clearance of poly(ethylene glycol)-modified
                    immunoenzyme with anti-PEG monoclonal
                    antibody for prodrug cancer therapy.
AUTHOR:             Cheng T L; Chen B M; Chern J W; Wu M F; Roffler S R
CORPORATE SOURCE:   Institute of Biomedical Sciences, Academia Sinica, Taipei,
```

Taiwan.
SOURCE: Bioconjugate chemistry, (2000 Mar-Apr) Vol. 11, No. 2, pp. 258-66.
Journal code: 9010319. ISSN: 1043-1802.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000613
Last Updated on STN: 20000613
Entered Medline: 20000531

L2 ANSWER 2 OF 4 MEDLINE on STN
ACCESSION NUMBER: 1998089627 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9428158
TITLE: Immobilization of L-asparaginase into a biocompatible poly(ethylene glycol)-albumin hydrogel: evaluation of performance in vivo.
AUTHOR: Jean-Francois J; D'Urso E M; Fortier G
CORPORATE SOURCE: Departement de Chimie-Biochimie, Universite du Quebec, Montreal, Canada.
SOURCE: Biotechnology and applied biochemistry, (1997 Dec) Vol. 26 (Pt 3), pp. 203-12.
Journal code: 8609465. ISSN: 0885-4513.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 20000303
Entered Medline: 19980205

L2 ANSWER 3 OF 4 MEDLINE on STN
ACCESSION NUMBER: 84160696 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6706424
TITLE: Polyethylene glycol reactive antibodies in man: titer distribution in allergic patients treated with monomethoxy polyethylene glycol modified allergens or placebo, and in healthy blood donors.
AUTHOR: Richter A W; Akerblom E
SOURCE: International archives of allergy and applied immunology, (1984) Vol. 74, No. 1, pp. 36-9.
Journal code: 0404561. ISSN: 0020-5915.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198405
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840522

L2 ANSWER 4 OF 4 MEDLINE on STN
ACCESSION NUMBER: 83107741 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6401699
TITLE: Antibodies against polyethylene glycol produced in animals by immunization with monomethoxy polyethylene glycol modified proteins.
AUTHOR: Richter A W; Akerblom E
SOURCE: International archives of allergy and applied immunology, (1983) Vol. 70, No. 2, pp. 124-31.

Journal code: 0404561. ISSN: 0020-5915.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198303
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19900318
Entered Medline: 19830311

=> d abs 3

L2 ANSWER 3 OF 4 MEDLINE on STN
AB Antibodies to polyethylene glycol (PEG) were analyzed in patients with various allergies and in healthy blood donors employing passive hemagglutination. In untreated allergic patients and in healthy blood donors, naturally occurring **anti-PEG** antibody titers between 32 and 512 were seen in 3.3 and 0.2%, respectively. During hyposensitization with monomethoxy polyethylene glycol modified ragweed extract and honey bee venom, respectively, the patients showed an **anti-PEG** antibody response. Titers of 32-512 were found in 50% of the patients directly after the first treatment course. After 2 years of treatment the percentage of patients with such titers declined to 28.5%. Mercaptoethanol treatment of sera indicated that the **anti -PEG** antibodies predominantly were of the IgM isotype. The weak IgM response found in treated patients is considered to be of no clinical significance.

=> s ABS 2
5100 ABS
3230499 2
L3 42 ABS 2
(ABS(W)2)

=> d abs l2 2

L2 ANSWER 2 OF 4 MEDLINE on STN
AB The L-asparaginase of Escherichia coli (ASNase) is currently used in combination with antineoplastic drugs to treat various lymphoblastic leukaemias. However, its use is limited by severe immunological reactions and the short serum half-life associated with the enzyme. Immobilization of ASNase into a biocompatible matrix can greatly decrease the immunogenicity of the enzyme, increase its half-life in vivo and its therapeutic index. Thus the E. coli ASNase was immobilized in a biocompatible hydrogel made of rat serum albumin and poly(ethylene glycol) (PEG; molecular mass 10 kDa). The effectiveness of this enzymic bioreactor to deplete serum L-asparagine was evaluated after its peritoneal implantation in rats. Seven units of immobilized ASNase/rat depleted serum asparagine to an undetectable level (< 1 microM) during 6 days, while 5 units of immobilized ASNase/rat decreased the level of serum asparagine by 85-90% during at least 2 days. Under both conditions asparagine levels returned to normal about 10 days after surgery, and hydrogels still retained 80% of their enzymic activity when assayed in vitro. After 10-14 days in vivo, hydrogels became opaque and surrounded by a fibrotic capsule with a few inflammatory sites. Nevertheless, the enzymic hydrogel showed great stability in vivo, and, after 4 months of implantation, 12% of the initial ASNase activity was still present. At 6 months, histological analysis showed stabilization of the fibrotic capsule thickness. Assays on the levels of ASNase and asparagine synthetase indicated an induction of the latter activity, mainly in the pancreas when compared with the level observed in spleen or liver. ELISA tests at 28

days and 120 days showed the presence of anti-ASNase (and, in lower amounts, **anti-PEG**) antibodies in sera of implanted rats. As observed with other enzyme-immobilization systems used in vivo, the formation of fibroblast-like cell layers around the implant, which block the translocation of the substrate into the enzymic matrix, is the major factor affecting the performance and longevity of the bioreactor.

```
=> s anti () (polyethylene glycol)
        616721 ANTI
             6 ANTIS
        616725 ANTI
                 (ANTI OR ANTIS)
         35662 POLYETHYLENE
          5898 POLYETHYLENES
         38703 POLYETHYLENE
                 (POLYETHYLENE OR POLYETHYLENES)
         23440 GLYCOL
         28763 GLYCOLS
         41826 GLYCOL
                 (GLYCOL OR GLYCOLS)
         23715 POLYETHYLENE GLYCOL
                 (POLYETHYLENE(W)GLYCOL)
L4           1 ANTI (W) (POLYETHYLENE GLYCOL)

=> d ibib

L4   ANSWER 1 OF 1     MEDLINE on STN
ACCESSION NUMBER:   1999278171     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 10346886
TITLE:              Accelerated clearance of polyethylene glycol-modified
                    proteins by anti-polyethylene
                    glycol IgM.
AUTHOR:             Cheng T L; Wu P Y; Wu M F; Chern J W; Roffler S R
CORPORATE SOURCE:   Institute of Biomedical Sciences, Academia Sinica, College
                    of Medicine, National Taiwan University, Taipei, Taiwan.
SOURCE:             Bioconjugate chemistry, (1999 May-Jun) Vol. 10, No. 3, pp.
                    520-8.
                    Journal code: 9010319. ISSN: 1043-1802.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199907
ENTRY DATE:         Entered STN: 19990715
                    Last Updated on STN: 19990715
                    Entered Medline: 19990707


=> s antibod? (against or to) (peg or (polyethylene glycol))
MISSING OPERATOR 'ANTIBOD? (AGAINST'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s antibod? (s) (against or to) (s) (peg or (polyethylene glycol))
        708410 ANTIBOD?
        455081 AGAINST
             6 AGAINSTS
        455085 AGAINST
                 (AGAINST OR AGAINSTS)
       7985384 TO
           859 TOS
       7985637 TO
```

```
                (TO OR TOS)
          9879 PEG
           777 PEGS
         10278 PEG
                (PEG OR PEGS)
         35662 POLYETHYLENE
          5898 POLYETHYLENES
         38703 POLYETHYLENE
                (POLYETHYLENE OR POLYETHYLENES)
         23440 GLYCOL
         28763 GLYCOLS
         41826 GLYCOL
                (GLYCOL OR GLYCOLS)
         23715 POLYETHYLENE GLYCOL
                (POLYETHYLENE(W)GLYCOL)
L5         456 ANTIBOD? (S) (AGAINST OR TO) (S) (PEG OR (POLYETHYLENE GLYCOL))

=> s clear? or remov?
        358107 CLEAR?
        281667 REMOV?
L6      626149 CLEAR? OR REMOV?

=> s l6 and l5
L7          68 L6 AND L5

=> s l7 not py>1999
       3443289 PY>1999
                (PY>19999999)
L8          49 L7 NOT PY>1999

=> d scan
'DISPLAY SCAN' IS NOT VALID IN CURRENT FILE

The DISPLAY SCAN command is not valid in the current file.
Enter HELP FORMATS and HELP DFIELDS to see valid DISPLAY
options in current file.

=> d l1

L1   ANSWER 1 OF 7     MEDLINE on STN
AN   2005175711     MEDLINE
DN   PubMed ID: 15809678
TI   Repeated injections of PEG-PE liposomes generate anti-
     PEG antibodies.
AU   Sroda Kamila; Rydlewski Janusz; Langner Marek; Kozubek Arkadiusz; Grzybek
     Michal; Sikorski Aleksander F
CS   Academic Centre for the Biotechnology of Lipid Aggregates,
     Przybyszewskiego 63/77, 51-148 Wroclaw, Poland.. afsbc@ibmb.uni.wroc.pl
SO   Cellular & molecular biology letters, (2005) Vol. 10, No. 1, pp. 37-47.
     Journal code: 9607427. ISSN: 1425-8153.
CY   Poland
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   200508
ED   Entered STN: 20050406
     Last Updated on STN: 20050806
     Entered Medline: 20050805


=> d l8 1

L8   ANSWER 1 OF 49     MEDLINE on STN
```

AN 1999333743 MEDLINE
DN PubMed ID: 10403934
TI Heat treatment of normal human sera reveals antibodies to bactericidal permeability-inducing protein (BPI).
AU Brownlee A A; Lockwood C M
CS University of Cambridge, School of Clinical Medicine, Addenbrooke's Hospital, Cambridge, UK.
SO Clinical and experimental immunology, (1999 Jul) Vol. 117, No. 1, pp. 183-9.
Journal code: 0057202. ISSN: 0009-9104.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199907
ED Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990728

=> d kwic

L8 ANSWER 1 OF 49 MEDLINE on STN
AB . . . was maximal at 56 degrees C, with substantial antibody demonstrable after only 5 min at this temperature. In experiments using **polyethylene glycol** (**PEG**)6000 **to** **remove** immune complexes, the effect of heating could be abrogated by preincubation with 8% **PEG**, which suggested that these anti BPI **antibodies** might be complexed in sera. After passage of normal plasma over a protein G column, the acid-eluted fraction contained elevated. . .

=> s antibod? (w) (against or to) (w) (peg or (polyethylene glycol))
708410 ANTIBOD?
455081 AGAINST
6 AGAINSTS
455085 AGAINST
(AGAINST OR AGAINSTS)
7985384 TO
859 TOS
7985637 TO
(TO OR TOS)
9879 PEG
777 PEGS
10278 PEG
(PEG OR PEGS)
35662 POLYETHYLENE
5898 POLYETHYLENES
38703 POLYETHYLENE
(POLYETHYLENE OR POLYETHYLENES)
23440 GLYCOL
28763 GLYCOLS
41826 GLYCOL
(GLYCOL OR GLYCOLS)
23715 POLYETHYLENE GLYCOL
(POLYETHYLENE(W)GLYCOL)
L9 11 ANTIBOD? (W) (AGAINST OR TO) (W) (PEG OR (POLYETHYLENE GLYCOL))

=> s l9 and l6
L10 0 L9 AND L6

=> s l9 not py>2000

2953639 PY>2000
(PY>20009999)
L11 8 L9 NOT PY>2000

=> d ibib 1-8

L11 ANSWER 1 OF 8 MEDLINE on STN
ACCESSION NUMBER: 1999382152 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10454349
TITLE: Detection and characterization of **antibodies to PEG**-IFN-alpha2b using surface plasmon resonance.
AUTHOR: Takacs M A; Jacobs S J; Bordens R M; Swanson S J
CORPORATE SOURCE: Schering-Plough Research Institute, Kenilworth, NJ 07033, USA.
SOURCE: Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research, (1999 Jul) Vol. 19, No. 7, pp. 781-9. Journal code: 9507088. ISSN: 1079-9907.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991101
Last Updated on STN: 19991101
Entered Medline: 19991019

L11 ANSWER 2 OF 8 MEDLINE on STN
ACCESSION NUMBER: 97431634 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9287139
TITLE: Immunoliposomes bearing polyethyleneglycol-coupled Fab' fragment show prolonged circulation time and high extravasation into targeted solid tumors in vivo.
AUTHOR: Maruyama K; Takahashi N; Tagawa T; Nagaike K; Iwatsuru M
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, Teikyo University, Kanagawa, Japan.. maruyama@pharm.teikyo-u.ac.jp
SOURCE: FEBS letters, (1997 Aug 11) Vol. 413, No. 1, pp. 177-80. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971030

L11 ANSWER 3 OF 8 MEDLINE on STN
ACCESSION NUMBER: 93165399 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8433874
TITLE: Enzyme replacement therapy with polyethylene glycol-adenosine deaminase in adenosine deaminase deficiency: overview and case reports of three patients, including two now receiving gene therapy.
AUTHOR: Hershfield M S; Chaffee S; Sorensen R U
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710.
CONTRACT NUMBER: DK20902 (NIDDK)
RR00080 (NCRR)
SOURCE: Pediatric research, (1993 Jan) Vol. 33, No. 1 Suppl, pp. S42-7; discussion S47-8. Ref: 19
Journal code: 0100714. ISSN: 0031-3998.

PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199303
ENTRY DATE: Entered STN: 19930402
Last Updated on STN: 19930402
Entered Medline: 19930318

L11 ANSWER 4 OF 8 MEDLINE on STN
ACCESSION NUMBER: 86007216 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2412977
TITLE: Studies on antigenicity of the polyethylene glycol (PEG)-modified uricase.
AUTHOR: Tsuji J; Hirose K; Kasahara E; Naitoh M; Yamamoto I
SOURCE: International journal of immunopharmacology, (1985) Vol. 7, No. 5, pp. 725-30.
Journal code: 7904799. ISSN: 0192-0561.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198511
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19851121

L11 ANSWER 5 OF 8 MEDLINE on STN
ACCESSION NUMBER: 85156525 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3980111
TITLE: Immune responses to polyethylene glycol modified L-asparaginase in mice.
AUTHOR: Kawamura K; Igarashi T; Fujii T; Kamisaki Y; Wada H; Kishimoto S
SOURCE: International archives of allergy and applied immunology, (1985) Vol. 76, No. 4, pp. 324-30.
Journal code: 0404561. ISSN: 0020-5915.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198505
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850513

L11 ANSWER 6 OF 8 MEDLINE on STN
ACCESSION NUMBER: 84160696 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6706424
TITLE: Polyethylene glycol reactive antibodies in man: titer distribution in allergic patients treated with monomethoxy polyethylene glycol modified allergens or placebo, and in healthy blood donors.
AUTHOR: Richter A W; Akerblom E
SOURCE: International archives of allergy and applied immunology, (1984) Vol. 74, No. 1, pp. 36-9.
Journal code: 0404561. ISSN: 0020-5915.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 198405
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840522

L11 ANSWER 7 OF 8 MEDLINE on STN
ACCESSION NUMBER: 83107741 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6401699
TITLE: **Antibodies against polyethylene glycol** produced in animals by immunization with monomethoxy polyethylene glycol modified proteins.
AUTHOR: Richter A W; Akerblom E
SOURCE: International archives of allergy and applied immunology, (1983) Vol. 70, No. 2, pp. 124-31.
Journal code: 0404561. ISSN: 0020-5915.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198303
ENTRY DATE: Entered STN: 19900318
Last Updated on STN: 19900318
Entered Medline: 19830311

L11 ANSWER 8 OF 8 MEDLINE on STN
ACCESSION NUMBER: 77187848 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16907
TITLE: Effect of covalent attachment of polyethylene glycol on immunogenicity and circulating life of bovine liver catalase.
AUTHOR: Abuchowski A; McCoy J R; Palczuk N C; van Es T; Davis F F
SOURCE: The Journal of biological chemistry, (1977 Jun 10) Vol. 252, No. 11, pp. 3582-6.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197707
ENTRY DATE: Entered STN: 19900314
Last Updated on STN: 19950206
Entered Medline: 19770723

=> d abs 8

L11 ANSWER 8 OF 8 MEDLINE on STN
AB Methoxypolyethylene glycols of 1900 daltons (PEG-1900) or 5000 daltons (PEG-5000) were covalently attached to bovine liver catalase using 2,4,6-trichloro-s-triazine as the coupling agent. Rabbits were immunized by the intravenous and intramuscular routes with catalase modified by covalent attachment of PEG-1900 to 43% of the amino groups (PEG-1900-catalase). The intravenous antiserum did not yield detectable **antibodies against PEG**-1900-catalase or native catalase, as determined by Ouchterlony and complement fixation methods, whereas the intramuscular antiserum contained antibodies to both PEG-1900-catalase and catalase. PEG-1900 did not react with either antiserum. Catalase was prepared in which PEG-5000 was attached to 40% of the amino groups (PEG-5000-catalase). This catalase preparation did not react with either antiserum. PEG-1900-catalase retained 93% of its enzymatic activity; PEG-5000-catalase retained 95%. PEG-5000-catalase resisted digestion by trypsin, chymotrypsin, and a protease from Streptomyces griseus. PEG-1900-catalase and PEG-5000-catalase exhibited

enhanced circulating lives in the blood of acatalasemic mice during repetitive intravenous injections. No evidence was seen of an immune response to injections of the modified enzymes. Mice injected repetitively with PEG-5000-catalase remained immune competent for unmodieied catalase, and no evidence of tissue or organ damage was seen.

```
=> file caplsu
'CAPLSU' IS NOT A VALID FILE NAME
SESSION CONTINUES IN FILE 'MEDLINE'
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       7.04       7.25

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FILE COVERS 1907 - 7 Mar 2006  VOL 144 ISS 11
FILE LAST UPDATED: 6 Mar 2006  (20060306/ED)

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=> s anti () PEG
        398531 ANTI
             9 ANTIS
        398538 ANTI
                 (ANTI OR ANTIS)
         35011 PEG
          1176 PEGS
         35503 PEG
                 (PEG OR PEGS)
L12         10 ANTI (W) PEG

=> s l12 not py>2000
       5537520 PY>2000
L13          5 L12 NOT PY>2000

=> d ibib 1-5

L13  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2000:334699  CAPLUS
```

TITLE: Bioactive poly(ethylene glycol)-insulin conjugates with enhanced stability and reduced immunogenicity.
AUTHOR(S): Hinds, Ken; Joss, Lisa; Rihova, Blanka; Koh, Jae Joon; Liu, Feng; Baudys, Miroslav; Kim, Sung Wan
CORPORATE SOURCE: Department of Pharmaceutics and Pharmaceutical Chemistry / CCCD, University of Utah, Salt Lake City, UT, 84112, USA
SOURCE: Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), POLY-511. American Chemical Society: Washington, D. C. CODEN: 69CLAC
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English

L13 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:125916 CAPLUS
DOCUMENT NUMBER: 132:298658
TITLE: Efficient Clearance of Polyethylene glycol-Modified Immunoenzyme with **Anti-PEG** Monoclonal Antibody for Prodrug Cancer Therapy
AUTHOR(S): Cheng, Tian-Lu; Chen, Bing-Mae; Chern, Ji-Wang; Wu, Ming-Fang; Roffler, Steve R.
CORPORATE SOURCE: Institute of Biomedical Sciences, Academia Sinica, School of Pharmacy National Taiwan University College of Medicine, Taipei, Taiwan
SOURCE: Bioconjugate Chemistry (2000), 11(2), 258-266 CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:239090 CAPLUS
DOCUMENT NUMBER: 131:63325
TITLE: Accelerated Clearance of Polyethylene Glycol-Modified Proteins by Anti-Polyethylene Glycol IgM
AUTHOR(S): Cheng, Tian-Lu; Wu, Pin-Yi; Wu, Ming-Fang; Chern, Ji-Wang; Roffler, Steve R.
CORPORATE SOURCE: Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan
SOURCE: Bioconjugate Chemistry (1999), 10(3), 520-528 CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:24552 CAPLUS
DOCUMENT NUMBER: 128:162592
TITLE: Immobilization of L-asparaginase into a biocompatible poly(ethylene glycol)-albumin hydrogel: evaluation of performance in vivo
AUTHOR(S): Jean-Francois, Jacques; D'urso, Edith Marie; Fortier, Guy
CORPORATE SOURCE: Laboratoire d'Enzymologie Appliquee, Departement de Chimie-Biochimie, Universite du Quebec, Montreal, Montreal, QC, H3C 3P8, Can.
SOURCE: Biotechnology and Applied Biochemistry (1997), 26(3), 203-212

CODEN: BABIEC; ISSN: 0885-4513
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1983:15249 CAPLUS
DOCUMENT NUMBER: 98:15249
TITLE: Antibodies against polyethylene glycol produced in animals by immunization with monomethoxy polyethylene glycol-modified proteins
AUTHOR(S): Richter, Ary Wolfgang; Aakerblom, Eva
CORPORATE SOURCE: Dep. Biomed. Res., Pharm. AB, Uppsala, 75104, Swed.
SOURCE: International Archives of Allergy and Applied Immunology (1983), 70(2), 124-31
CODEN: IAAAAM; ISSN: 0020-5915
DOCUMENT TYPE: Journal
LANGUAGE: English

```
=> s antibod? (w) (against or to) (w) (peg or (polyethylene glycol))
        455631 ANTIBOD?
        678912 AGAINST
            37 AGAINSTS
        678927 AGAINST
                 (AGAINST OR AGAINSTS)
             0 TO
          1364 TOS
          1364 TO
                 (TO OR TOS)
         35011 PEG
          1176 PEGS
         35503 PEG
                 (PEG OR PEGS)
        338433 POLYETHYLENE
         12590 POLYETHYLENES
        342295 POLYETHYLENE
                 (POLYETHYLENE OR POLYETHYLENES)
        344776 GLYCOL
         44765 GLYCOLS
        360101 GLYCOL
                 (GLYCOL OR GLYCOLS)
         97872 POLYETHYLENE GLYCOL
                 (POLYETHYLENE(W)GLYCOL)
L14          4 ANTIBOD? (W) (AGAINST OR TO) (W) (PEG OR (POLYETHYLENE GLYCOL))

=> d ibib 1-4
```

L14 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:191308 CAPLUS
TITLE: Control of hyperuricemia in subjects with refractory gout, and induction of antibody against poly(ethylene) glycol (PEG), in a phase I trial of subcutaneous PEGylated urate oxidase
AUTHOR(S): Ganson, Nancy J.; Kelly, Susan J.; Scarlett, Edna; Sundy, John S.; Hershfield, Michael S.
CORPORATE SOURCE: Division of Rheumatology, Duke University Medical Center, Durham, NC, 27710, USA
SOURCE: Arthritis Research & Therapy (2006), 8(1), No pp. given
CODEN: ARTRCV; ISSN: 1478-6362

URL: http://arthritis-research.com/content/pdf/ar1861.pdf
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

L14 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1985:539940 CAPLUS
DOCUMENT NUMBER: 103:139940
TITLE: Studies on antigenicity of the polyethylene glycol (PEG)-modified uricase
AUTHOR(S): Tsuji, Junichi; Hirose, Katsumi; Kasahara, Etsuko; Naitoh, Maki; Yamamoto, Itaru
CORPORATE SOURCE: Toyobo Res. Cent., Toyobo Co., Ltd., Ohtsu, 520-02, Japan
SOURCE: International Journal of Immunopharmacology (1985), 7(5), 725-30
CODEN: IJIMDS; ISSN: 0192-0561
DOCUMENT TYPE: Journal
LANGUAGE: English

L14 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1983:15249 CAPLUS
DOCUMENT NUMBER: 98:15249
TITLE: **Antibodies against polyethylene glycol** produced in animals by immunization with monomethoxy polyethylene glycol-modified proteins
AUTHOR(S): Richter, Ary Wolfgang; Aakerblom, Eva
CORPORATE SOURCE: Dep. Biomed. Res., Pharm. AB, Uppsala, 75104, Swed.
SOURCE: International Archives of Allergy and Applied Immunology (1983), 70(2), 124-31
CODEN: IAAAAM; ISSN: 0020-5915
DOCUMENT TYPE: Journal
LANGUAGE: English

L14 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1977:449460 CAPLUS
DOCUMENT NUMBER: 87:49460
TITLE: Effect of covalent attachment of polyethylene glycol on immunogenicity and circulating life of bovine liver catalase
AUTHOR(S): Abuchowski, Abraham; McCoy, John R.; Palczuk, Nicholas C.; Van Es, Theo; Davis, Frank F.
CORPORATE SOURCE: Dep. Biochem., Rutgers, State Univ., New Brunswick, NJ, USA
SOURCE: Journal of Biological Chemistry (1977), 252(11), 3582-6
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

=> s clear? or remov?
437130 CLEAR?
1200397 REMOV?
L15 1611632 CLEAR? OR REMOV?

=> s l15 and l14
L16 0 L15 AND L14

=> s l14 and retent? or retain?
179765 RETENT?

```
        195985 RETAIN?
L17     195985 L14 AND RETENT? OR RETAIN?

=> s l14 and (retent? or retain?)
        179765 RETENT?
        195985 RETAIN?
L18          1 L14 AND (RETENT? OR RETAIN?)

=> d ibib

L18  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1977:449460  CAPLUS
DOCUMENT NUMBER:          87:49460
TITLE:                    Effect of covalent attachment of polyethylene glycol
                          on immunogenicity and circulating life of bovine liver
                          catalase
AUTHOR(S):                Abuchowski, Abraham; McCoy, John R.; Palczuk, Nicholas
                          C.; Van Es, Theo; Davis, Frank F.
CORPORATE SOURCE:         Dep. Biochem., Rutgers, State Univ., New Brunswick,
                          NJ, USA
SOURCE:                   Journal of Biological Chemistry (1977), 252(11),
                          3582-6
                          CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE:            Journal
LANGUAGE:                 English


=> d abs kwic

L18  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
AB   Methoxypolyethylene glycols of 1900 daltons (PEG-1900) or 5000 daltons
     (PEG-5000) were covalently attached to bovine liver catalase (I) using
     2,4,6-trichloro-s-triazine as the coupling agent.  Rabbits were immunized
     i.v. and i.m. with I modified by covalent attachment of PEG-1900 to 43% of
     the NH2 groups (PEG-1900-I).  The i.v. antiserum had no detectable
     antibodies against PEG-1900-I or native I,
     whereas the i.m. antiserum contained antibodies to both PEG-1900-I and I.
     PEG-1900 did not react with either antiserum.  I was prepared in which
     PEG-5000 was attached to 40% of the NH2 groups (PEG-5000-I).  This I
     preparation did not react with either antiserum.  PEG-1900-I retained
     93% of its activity; PEG-5000-I retained 95%.  PEG-5000-I
     resisted digestion by trypsin, chymotrypsin, and a protease from
     Streptomyces griseus.  PEG-1900-I and PEG-5000-I had enhanced circulating
     lives in the blood of acatalasemic mice during repetitive i.v. injections.
     No evidence was seen of an immune response to injections of the modified
     I.  Mice injected repetitively with PEG-5000-I remained immune competent
     for unmodified I, and no evidence of tissue or organ damage was seen.
AB   . . .  I modified by covalent attachment of PEG-1900 to 43% of the NH2
     groups (PEG-1900-I).  The i.v. antiserum had no detectable
     antibodies against PEG-1900-I or native I,
     whereas the i.m. antiserum contained antibodies to both PEG-1900-I and I.
     PEG-1900 did not react with either.  . .  PEG-5000 was attached to 40% of
     the NH2 groups (PEG-5000-I).  This I preparation did not react with either
     antiserum.  PEG-1900-I retained 93% of its activity; PEG-5000-I
     retained 95%.  PEG-5000-I resisted digestion by trypsin,
     chymotrypsin, and a protease from Streptomyces griseus.  PEG-1900-I and
     PEG-5000-I had enhanced circulating lives.  . .


=> file pctfull
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              44.55      51.80
```

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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -0.75      -0.75

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FILE LAST UPDATED:          05 MAR 2006      <20060305/UPTX>
MOST RECENT UPDATE WEEK:         200608
FILE COVERS 1978 TO DATE

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>>> UPDATING OF BIBLIOGRAPHIC DATA DELAYED DUE TO DELIVERY
    FORMAT CHANGES <<<

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    ONLY, USE FIELD CODE FPI <<<

>>> SDI SEARCHES (ALERTS) WILL BE RESUMED WHEN BIBLIOGRAPHIC DATA
    BECOME AVAILABLE <<<

=> s anti () PEG
        170585 ANTI
           169 ANTIS
        170619 ANTI
                  (ANTI OR ANTIS)
         35845 PEG
          5031 PEGS
         38005 PEG
                  (PEG OR PEGS)
L19          7 ANTI (W) PEG

=> s l19 not py>2000
        550224 PY>2000
L20          0 L19 NOT PY>2000

=> s antibod? (w) (against or to) (w) (peg or (polyethylene glycol))
         85695 ANTIBOD?
        344502 AGAINST
            14 AGAINSTS
        344503 AGAINST
                  (AGAINST OR AGAINSTS)
       1040820 TO
          3118 TOS
       1040871 TO
                  (TO OR TOS)
         35845 PEG
          5031 PEGS
         38005 PEG
                  (PEG OR PEGS)
        132183 POLYETHYLENE
          5725 POLYETHYLENES
        132985 POLYETHYLENE
                  (POLYETHYLENE OR POLYETHYLENES)
        106336 GLYCOL
         41630 GLYCOLS
        113363 GLYCOL
```

```
                (GLYCOL OR GLYCOLS)
         67563 POLYETHYLENE GLYCOL
                (POLYETHYLENE(W)GLYCOL)
L21         15 ANTIBOD? (W) (AGAINST OR TO) (W) (PEG OR (POLYETHYLENE GLYCOL))

=> s l15 not py>2000
        303559 CLEAR?
        489065 REMOV?
        550224 PY>2000
L22     293482 L15 NOT PY>2000

=> s l21 not py>2000
        550224 PY>2000
L23          5 L21 NOT PY>2000

=> d ibib 1-5

L23    ANSWER 1 OF 5     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       2006017355 PCTFULL
       no bibliographic data available - please use FPI for PI information
DESIGNATED STATES

L23    ANSWER 2 OF 5     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       2000024770 PCTFULL  ED 20020515
TITLE (ENGLISH):        DIMERIC THROMBOPOIETIN PEPTIDE MIMETICS BINDING TO MP1
                        RECEPTOR AND HAVING THROMBOPOIETIC ACTIVITY
TITLE (FRENCH):         COMPOSES THROMBOPOIETIQUES
INVENTOR(S):            LIU, Chuan-Fa;
                        FEIGE, Ulrich;
                        CHEETHAM, Janet
PATENT ASSIGNEE(S):     AMGEN INC.
LANGUAGE OF PUBL.:      English
DOCUMENT TYPE:          Patent
PATENT INFORMATION:
                        NUMBER              KIND     DATE
                        ---------------------------------
                        WO 2000024770         A2 20000504
DESIGNATED STATES
       W:               AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE
                        DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE
                        KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX
                        NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA
                        UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM
                        AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB
                        GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML
                        MR NE SN TD TG
APPLICATION INFO.:      WO 1999-US24834       A  19991022
PRIORITY INFO.:         US 1998-60/105,348       19981023

L23    ANSWER 3 OF 5     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       1995004159 PCTFULL  ED 20020514
TITLE (ENGLISH):        BLOOD LEAD DIAGNOSTIC ASSAY
TITLE (FRENCH):         PROCEDE DIAGNOSTIQUE DE DETERMINATION DE LA PRESENCE DE
                        PLOMB DANS LE SANG
INVENTOR(S):            JAFFE, Eileen, K.
PATENT ASSIGNEE(S):     FOX CHASE CANCER CENTER
DOCUMENT TYPE:          Patent
PATENT INFORMATION:
                        NUMBER              KIND     DATE
                        ---------------------------------
                        WO 9504159            A1 19950209
DESIGNATED STATES
       W:               CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
```

APPLICATION INFO.: WO 1994-US8626 A 19940802
PRIORITY INFO.: US 1993-8/100,980 19930803

L23 ANSWER 4 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1993008838 PCTFULL ED 20020513
TITLE (ENGLISH): ORAL PHARMACEUTICAL COMPOSITION CONTAINING POLYETHYLENE GLYCOL IMMUNOGLOBULIN CONJUGATE
TITLE (FRENCH): COMPOSITION PHARMACEUTIQUE ORALE CONTENANT UN CONJUGUE D'IMMUNOGLOBULINE DE POLYETHYLENE GLYCOL
INVENTOR(S): CUNNINGHAM-RUNDLES, Charlotte
PATENT ASSIGNEE(S): MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9308838	A1	19930513

DESIGNATED STATES
W: AU CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL SE
APPLICATION INFO.: WO 1992-US8784 A 19921015
PRIORITY INFO.: US 1991-7/783,360 19911028

L23 ANSWER 5 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1993000109 PCTFULL ED 20020513
TITLE (ENGLISH): METHOD OF STIMULATING IMMUNE RESPONSE USING GROWTH HORMONE
TITLE (FRENCH): PROCEDE DE STIMULATION DE LA REPONSE IMMUNITAIRE A L'AIDE D'HORMONE DE CROISSANCE
INVENTOR(S): CARLSSON, Lena, Mariana, Susann;
CLARK, Ross, G.;
CRONIN, Michael, J.;
JARDIEU, Paula, M.
PATENT ASSIGNEE(S): GENENTECH, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9300109	A1	19930107

DESIGNATED STATES
W: AU CA JP AT BE CH DE DK ES FR GB GR IT LU MC NL SE
APPLICATION INFO.: WO 1992-US4489 A 19920529
PRIORITY INFO.: US 1991-723,359 19910628

=> d kwic 5

L23 ANSWER 5 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . antigen did not yield detectable antibodies against P EG-1 900-catalase or native
catalase whereas the antiserum from intramuscular administered antigen contained **antibodies**
to PEG catalase and native catalase. PEG catalase did not react with either
antiserum.

=> d kwic 1-5

L23 ANSWER 1 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . measured using a sandwich ELISA that utilizes a capture antibody to
aprotinin (produced as described in Example 6) and a reporter
antibody to PEG (e.g., AGP3 from
Acadmica Sinica). Aprotinin variant plasma levels may also be measured using radiolabeled
aprotinin variants (e.g., Shin, Pharm. Pharmcol. Commun.. . .

L23 ANSWER 2 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . In contrast, treatment in the various cycles with PEG-rHuMGDF did show
an inhibition in platelet response by Cycle 4, suggesting that
antibodies to PEG-
rHuMGDF have been generated and these anti-MGDF antibodies may be
i h endogenous rhesus TPO.

L23 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD Polyclonal **antibodies to PEGS** can be made
with the purified protein using methods known in the art. Antibodies are raised in suitable animals such. . .

L23 ANSWER 4 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . 42,0 to 79,6 percent of
that found for native IgG,
Example 12
Since in several of the above methods the binding
of a second **antibody to PEG**-IgG conjugates
to determine
the biologic activities of these conjugates was used to
compare PEG-IgG conjugates to native IgG, experiments
to determine the relative. . .
. . .
equal
concentrations (22,5 gg/ml); similar data were found
for other concentrations of IgG tested, 225 gg/ml and
2.25 ggfml)
TABLE 7
BINDING OF A SECOND **ANTIBODY**
TO PEG-IgG CONJUGATES
% of Control
IgG Bound % of Control
IgG to ELISA IgG Detected
,Compound Plate* in Solution**
Native IgG 100 100
Conjugates.

L23 ANSWER 5 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . antigen did not yield detectable antibodies against P EG-1 900-catalase or native
catalase whereas the antiserum from intramuscular administered antigen
contained **antibodies**
to PEG catalase and native catalase. PEG catalase
did not react with either
antiserum.

=> d his

(FILE 'HOME' ENTERED AT 10:47:25 ON 07 MAR 2006)

```
     FILE 'MEDLINE' ENTERED AT 10:47:38 ON 07 MAR 2006
L1             7 S ANTI () PEG
L2             4 S L1 NOT PY>2000
L3            42 S ABS 2
L4             1 S ANTI () (POLYETHYLENE GLYCOL)
L5           456 S ANTIBOD? (S) (AGAINST OR TO) (S) (PEG OR (POLYETHYLENE GLYCOL
L6        626149 S CLEAR? OR REMOV?
L7            68 S L6 AND L5
L8            49 S L7 NOT PY>1999
L9            11 S ANTIBOD? (W) (AGAINST OR TO) (W) (PEG OR (POLYETHYLENE GLYCOL
L10            0 S L9 AND L6
L11            8 S L9 NOT PY>2000

     FILE 'CAPLUS' ENTERED AT 10:54:30 ON 07 MAR 2006
L12           10 S ANTI () PEG
L13            5 S L12 NOT PY>2000
L14            4 S ANTIBOD? (W) (AGAINST OR TO) (W) (PEG OR (POLYETHYLENE GLYCOL
L15      1611632 S CLEAR? OR REMOV?
L16            0 S L15 AND L14
L17       195985 S L14 AND RETENT? OR RETAIN?
L18            1 S L14 AND (RETENT? OR RETAIN?)

     FILE 'PCTFULL' ENTERED AT 10:57:26 ON 07 MAR 2006
L19            7 S ANTI () PEG
L20            0 S L19 NOT PY>2000
L21           15 S ANTIBOD? (W) (AGAINST OR TO) (W) (PEG OR (POLYETHYLENE GLYCOL
L22       293482 S L15 NOT PY>2000
L23            5 S L21 NOT PY>2000

=> s clear? or remov?
        303559 CLEAR?
        489065 REMOV?
L24     578709 CLEAR? OR REMOV?

=> s l24 and l23
L25            5 L24 AND L23

=> d kwic 1-5

L25    ANSWER 1 OF 5     PCTFULL   COPYRIGHT 2006 Univentio on STN

DETD  . . . per molecule, denaturing the
       double-stranded DNA, renaturing the DNA to form double-stranded DNA
       which can include
       sense/antisense pairs from different nicked products, removing
       single-stranded portions from
       8
       reformed duplexes by treatment with S1 nuclease, and ligating the
       resulting fragment library into
       an expression vector. By this. . .
 . . .
       chain protected peptide may be cleaved with a base and the appropriate
       alcohol (e.g., methanol). Side chain protecting groups may be
       removed in the usual fashion by
       treatment with hydrogen fluoride to obtain the desired ester. In
       preparing peptide mimetics
       wherein the C-terminall carboxyl. . . dialkylamide (i.e., the
       C-terminus is --
       C(O)NRR,, where R and R, are alkyl, a lower alkyl). Side chain
       protection is then removed in the
       usual fashion by treatment with hydrogen fluoride to give the free
       amides, alkylamides, or
```

dialkylamides.

. . .
measured using a sandwich ELISA that utilizes a capture antibody to aprotinin (produced as described in Example 6) and a reporter **antibody to PEG** (e.g., AGP3 from Acadmica Sinica). Aprotinin variant plasma levels may also be measured using radiolabeled aprotinin variants (e.g., Shin, Pharm. Pharmcol. Commun.. . .

. . .
(80 mg/kg, i.p.) and treated with aprotinin (1 0 mg/kg, !.v.). Ten minutes later, the distal 2 mm of tail is **removed** and placed in to saline. The time for bleeding to stop is measured. Aprotinin and active variants reduce the bleeding time. . .

L25 ANSWER 2 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD Various studies using animal models (Ulich, TR. et al., Blood 86:971-976 (1995); Hokorn, M.M. et al., Blood 86:4486-4492 (1995)) have **clearly** demonstrated the therapeutic efficacies of TPO and MGDF in bone marrow transplantation and in the treatment of thrombocytopenia, a condition that often. . .

Even if the Cys residues that normally form disulfide bonds in the Fe dimer are **removed** or replaced by other residues, the monomeric chains will generally dimerize through non-covalent interactions. The term Fe herein is used to. . .

In Fe deletion variants, one or more amino acid residues in an Fe polypeptide are **removed**. Deletions can be effected at one or both termini of the Fe polypeptide, or with **removal** of one or more residues within the Fe amino acid sequence. Deletion variants, therefore, include all fragments of an Fe polypeptide. . .

In Fe substitution variants, one or more amino acid residues of an Fe polypeptide are **removed** and replaced with alternative residues. In one aspect, the substitutions are conservative in nature, however, the invention embraces substitutions that ore also. . .

. . .
the Fe sequences. In 21 particular, the amino acids at positions 7 and 10 of SEQ ID NO:5 are cysteine residues. One may **remove** each of these cysteine residues or substitute one or more such cysteine residues with other amino acids, such as Ala or. . .

. . .
oil of theobroma. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo **clearance** of the present proteins and derivatives. See, e.g., Remington's Phan-naceutical Sciences, 18th Ed. (I 990, Mack Publishing Co., Easton, PA 18042) pages. . .

. . .
incorporated by reference. Such formulations may influence the physical state, stability, rate of in Wvo release, and rate of in vivo **clearance** of the

administered agents. Depending on the route of administration, a suitable dose
may be calculated according to body weight, body surface. . .
. . .
used for side chain protection of the Lys on the linker and Boc-Ile-OH was
used for the last coupling. Dde was **removed** by using anhydrous hydrazine (2% in
NMP, 3x2min), followed by coupling with bromoacetic anhydride preformed by the
action of DCC. For peptide. . . was
effected at RT for 4 hr, using trifluoroacetic acid (TFA) containing 2.5% H20, 5%
phenol, 2.5% triisopropylsilane and 2.5% thioanisole. After **removal** of TFA, the
cleaved peptide was precipitated with cold anhydrous ether. Disulfide formation of
the cyclic peptide was performed directly on the. . .

Clearly, the activity of the tandem linked dimers may also depend on proper
selection of the length and composition of the linker. . .
. . .
second monomer) and parallel dimers (D terminal of first monomer linked to C terminal of second monomer) in the same assay **clearly** demonstrated the
superiority of tandem dimerized product compared to parallel dimer products. It is
interesting to note that a wide range of. . .
. . .
protection of the lysine E-amine. Once
the whole peptide chain was assembled, the N-terminal amine was reprotected with
t-Boc. Dde was then **removed** to allow for the bromoacetylation. This strategy gave
a high quality crude peptide which was easily purified using conventional reverse
phase HPLC.. . .
. . .
5 M urea, pH 9. The
pH of this mixture was then adjusted to pH 5 with acetic acid. The precipitate was
removed by centrifugation and the supernatant was loaded onto a SP-Sepharose
Fast Flow column equilibrated in 20 mM NaAc, 100 mM NaCl,. . .
. . .
enhance the in vivo
activity of the modified peptide by providing it a protection against proteolytic
degradation and by slowing down its **clearance** through renal filtration. It was
unexpected that pegylation could further increase the in vitro bioactivity of a tandem
dimerized TNIP peptide in. . .
. . .
In contrast, treatment in the various cycles with PEG-rHuMGDF did show an inhibition in platelet response by Cycle 4, suggesting that **antibodies to PEG-**
rHuMGDF have been generated and these anti-MGDF antibodies may be i h endogenous rhesus TPO.

L25 ANSWER 3 OF 5 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . the lungs or digestive tract and once ingested, lead accumulates in
bones and teeth. Long-term chelation therapy can be used to **remove** lead from bone tissue. However, if lead poisoning is untreated, the sequestered lead in bone tissue can be reintroduced into. . .

The present invention includes the step of isolating PEGS from the sample, thereby **removing** the confounding effect of interfering substances in the sample composition. The use of PEGS as a biological marker is an. . .

. . .
and 10"8 M in hemolysate (P.N.B. Gibbs, A-G. Chaudhry and P.M. Jordan, Biochem. J. 230:25-34 (1985)), PEGS can be quantitatively **removed** from a hemolysate sample using monoclonal or polyclonal antibodies. PEGS can be isolated from the blood of a test subject using antibodies. . .

Polyclonal **antibodies to PEGS** can be made with the purified protein using methods known in the art. Antibodies are raised in suitable animals such. . .

. . .
PEGS for raising antibodies may be isolated from outdated blood by a method which uses a batch extraction technique to **remove** the hemoglobin (P.N.B. Gibbs, A-G. Chaudhry and P.M. Jordan, Biochem. J

(b) Lead-inhibited PEGS would be distinguished from active PEGS as follows :
The double dipstick would be **removed** from the first vessel, split in half, and each individual dipstick, labelled either A or B, would be placed in a. . .

. . .
reaction would be allowed to proceed for a short period of time, approximately five minutes. Alternatively, the dipsticks could be **removed** to a third vessel containing, respectively, Buffer A plus 10 ALA and Buffer B plus ALA

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DETD . . . is dissolved in
a basic buffer solution, for example 0,01 M sodium phosphate buffer, pH 7,8, and then dialyzed against the buffer to **remove** residual salts. The concentrated serum Ig is then combined with activated PEG which can be obtained by a chemical process involving either 1,11-carbonyldiimidazole,. . .

. . .
serum immunoglobulin G in 0,01 M sodium phosphate buffer at pH 7*8. The resulting solution was then dialyzed against the buffer to **remove** residual salts. Determination of the final concentration of the immunoglobulin G was done spectrophotometrically using an extinction coefficient of 138 as E45 for. . .

50) to **remove** residual carbonyldiimidazole, The resulting activated PEG solution was dialyzed against distilled water, lyophilized, and stored desiccated,
Example 3
Activated PEG produced by the method. . .

. . .
15 g SS-PEG, The mixture is stirred for 30 min at room-temperature and clarified by Millipore filtration (1.2 gm membrane), Unbound SS-PEG

is **removed** by dialysis against 10 volumes of buffer using an Amicon cell as described above, Each preparation of PEG-IgG is sterilized by filtration. . .

. . .

Heat aggregated
human IgG and PEG-conjugates were produced by heating 10 mg/ml solutions of each in PBS to 630 for 30 minutes, After **removing** the largest (visible) aggregates by brief centrifugation (3,000 rpm from 5 minutes) the aggregates contained in the supernatants of these solutions were used. . .

. . .

42,0 to 79,6 percent of
that found for native IgG,
Example 12
Since in several of the above methods the binding of a second **antibody to PEG**-IgG conjugates to determine
the biologic activities of these conjugates was used to compare PEG-IgG conjugates to native IgG, experiments to determine the relative. . .

. . .

buffer, pH 4,5 with pepsin (Worthington Biochemical Corp,, Free Hold, NJ,) at an enzyme substrate ratio of 1:100, In one experiment, aliquots were **removed** from the reaction mixture at 1, 3f 51 7f 9 and 16 hours; in another, all reactions were stopped in 6 hours,. . .

. . .

equal
concentrations (22,5 gg/ml); similar data were found for other concentrations of IgG tested, 225 gg/ml and 2.25 ggfml)
TABLE 7
BINDING OF A SECOND **ANTIBODY**
TO PEG-IgG CONJUGATES
% of Control
IgG Bound % of Control
IgG to ELISA IgG Detected
,Compound Plate* in Solution**
Native IgG 100 100
Conjugates.

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DETD . . . tolerate. The short half-
life of hGH is believed to be due to its small molecular weight (22,000 dafton), and rapid renal
clearance, which has been found to be proportional to the molecular weight of protein in
35 circulation. Pegylation, meaning conjugating polyethylene glycol. .

. . .

bovine serum
albumin exhibited a blood circulating life in rabbits similar to native bovine serum albumin
go except that it was not **removed** from circulation by the eventual development of antibodies.

. . .

antigen did not yield detectable antibodies against P EG-1 900-catalase or native
catalase whereas the antiserum from intramuscular administered antigen contained **antibodies**

to PEG catalase and native catalase. PEG catalase did not react with either antiserum.

. . .

attached polymers such as polyethelene glycol, polypropylene glycol or carbohydrates; and 3) other macromolecules such as proteins, lipids, or glycolipids that reduce **clearance** and are not immunogenic.

. . .

the continuous presence of GH when the GH is complexed with itself or with another macromolecule such that the GH is not **cleared** from the plasma. Intermittent GH use is defined as administration every 3 or more days, preferably every 6 or more days.. . .

The present invention **clearly** shows that the s.c. administration of hGH as a continuous infusion or PEG-GH as daily or infrequent intermittent injections are optimal. . .

Therefore, R is **clear** that at this dose of hGH (0.1 mg/kglday) continuous administration and daily injection have equal effects on whole body weight gain.. . .

. . .

and that the difference could be due to the GHBP giving a lo more continuous OH exposure and a larger response. **Clearly** the rate of weight gain for hGH plus GHBP is substantially greater. This increased spleen weight gain is also plotted as. . .

. . .

growth of the thymus. This large absolute and relative growth response may be due to the met-hGH delivered by injections being **cleared** rapidly from the body whereas the PEG-hGH molecules are **cleared** more slowly and leads to a relative continuous GH exposure.

At sacrifice, a blood sample was taken, and the liver, kidneys, heart, spleen, and thymus were **removed**, blotted dry, and immediately weighed. The spleen and thymus were immediately placed in buff er and then cells were obtained by. . .

. . .

treated rats gained 34.5 + 9.4 g, and IGF and GH-treated rats gained 45.5 9.9 g. The response to IGR was **clearly** large, and the response to GH plus IGR appeared to be additive. IGR at the doses used was markedly anabolic. A. . .

The effect of IGR was **clearly** greater than that of hGH.

There was a **clear** effect of IGR on all the organ weights. Liver increased by 6.6%, kidneys by 16.6%, heart by 18.5%, thymus by 27.0%,. . .

30 Using this scheme characteristic, thymic involution was seen in the excipient and the GH-treated groups. However, there was **clear** evidence of lymphocytic hyperplasia and the restoration of the thymic architecture in the groups that received des-IGF-I and des-IGF-I plus

bGH. The. . .

. . .
blood
sample was taken, and the thymus, spleen, heart, liver, kidney, and mandibular and
mesenteric lymph nodes from each treatment group were **removed** aseptically and weighed.

. . .
growth of the spleen and the thymus after 7 days of
treatment with IGF-I. In the first experiment there was a **clear** dose-related effect of IGR on
the spleen (excipient 105 ± 14, low dose 124 + 21; medium dose
145 ± 58;. . . experiment; this was probably due to the thymus being dissected
differently by different dissectors. In the repeat experiment, one dissector uniformly **removed**
the thymus, and significant thymic growth was detected (excipient, 15.2
± 1.3; high dose 26.2
3o 6.4 mg, p = 0.006).

Femurs and tibias were **removed** from 40 donor animals. The bone marrow was
flushed out with PBS. Cells were centrif uged and washed with saline. Viable. . .

. . .
at this time. The remaining animals were sacrif iced 23 days after the irradiation
treatment. Spleens, thymuses, livers, and hearts were **removed** and weighed. Long bones
were taken for histology and the spleens and thymuses retained for cytological and in vitro
assays. Blood was. . .

. . .
92.0+8.3
IGF-I high 27.3+10.9* 1 51.2+9.3**. 1 125.0+35.4* 103.6+19.4
p < 0.05 of Marrow Only on same day
P < 0.01
15
There was a **clear** effect of IGR increasing thymus and spleen weight in this model.

The body weight changes for all four groups are shown in Figure 21. The figure shows
clearly the very large weight loss in the animals following radiation exposure. There was a
clear dose-related effect of IGR protecting the mice from this catabolism. High-dosb IGR
had a significant anabolic effect as early as seven. . .

. . .
is as an immunoadjuvant. Whenever
immunizing a mammal or avian, priming with GH and or IGR to accelerate the immunization
process is **clearly** indicated in the present invention.

CLMEN. . . of claim 1 wherein said method is accomplished using a growth hormone
complexed to one or more macromolecules to reduce GH **clearance** from the blood plasma.